1: Clin Cardiol 1995 Sep;18(9 Suppl 4):IV20-7

Tumor necrosis factor-alpha and the failing human heart.

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Tumor necrosis factor-alpha (TNF alpha) is a proinflammatory cytokine with negative inotropic effects. Recently, elevated levels of TNF alpha have been identified in patients with advanced heart failure. Although the clinical significance of this finding is unclear at present, there is increasing evidence that this cytokine may play a primary pathophysiologic role in the development and pathogenesis of heart failure in humans. Indeed, many of the clinical hallmarks of heart failure, including left ventricular dysfunction, cardiomyopathy, and pulmonary edema can be explained by the known biological effects of TNF alpha in humans. The present review will summarize recent evidence with regard to the biological role for TNF alpha in the adult mammalian heart, as well as summarize the increasing body of clinical information that implicates this cytokine in the pathophysiology of heart failure.

Publication Types:
- Review
- Review, Tutorial

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1: Pharmacol Ther 2002 Apr-May;94(1-2):123

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Tumor necrosis factor-alpha in cardiovascular biology and the potential role for anti-tumor necrosis factor-alpha therapy in heart disease.

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The functional role of tumor necrosis factor (TNF)-alpha in the heart has been extensively studied over the last 15 years. Collectively, these studies have demonstrated that TNF-alpha has both diverse and potentially conflicting roles in cardiac function and pathology. These include beneficial effects, such as cardioprotection against ischemia, myocarditis, and pressure overload, as well as potentially adverse effects, such as the development of atherosclerosis, reperfusion injury, hypertrophy, and heart failure. TNF-alpha antagonist therapy recently has been demonstrated to be clinically applicable in inflammatory conditions, and clinical trials are currently in progress in the use of these agents in cardiovascular diseases. The scope for clinical applications of anti-TNF-alpha therapy in cardiovascular diseases is potentially extensive. Hence, this review has been undertaken to evaluate the cardiovascular effects of this pleiotropic cytokine and to evaluate the potential of targeting this cytokine in cardiovascular therapeutics. An overview of the TNF-alpha peptide and its associated signaling are described. This is followed by a discussion of the known roles of TNF-alpha in cardiac physiology and in a diverse array of cardiac pathologies. Reference to experimental and clinical studies using anti-TNF-alpha therapies are described where applicable. The postulated role of TNF-alpha signaling concerning innate cardiac cellular processes that may have direct adaptive effects in the heart will be reviewed with respect to future research directions. Finally, the author postulates that attenuation of TNF-alpha biosynthesis in selected individuals will need to be tested if true benefits of this therapeutic approach are to be realized in the management of cardiovascular diseases.

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Targeting tumor necrosis factor alpha. New drugs used to modulate inflammatory diseases.

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Since its discovery, the understanding of the roles for TNF-alpha in human biology and disease has grown. Receptors for TNF are found on virtually all cell types, and many physiologic processes seem to be altered by TNF-alpha. The understanding of how TNF-alpha is involved in the pathophysiology of diseases, such as inflammatory diseases, has allowed the development of new drugs that can interfere with excess TNF-alpha and thus has allowed novel therapies for rheumatoid arthritis and Crohn's disease. As the role of TNF-alpha in other diseases becomes better understood, such TNF-alpha-modulating drugs may find further applications. In the skin, TNF-alpha is prominent cytokine that seems to be important in allergic and irritant contact dermatitis and inflammatory skin conditions. Modulating TNF-alpha activity in the skin may provide therapeutic benefits for a variety of skin conditions (Table 4). Tumor necrosis factor-alpha levels are elevated in skin lesions of psoriasis. A few reports have already suggested that etanercept and infliximab may offer a therapeutic effect in patients with psoriasis. Clinical studies evaluating the true efficacy of these drugs in psoriasis are under way. Specifically, the authors and others are involved in a double-blind, placebo-controlled study to assess the efficacy of etanercept for psoriasis. Thalidomide has been used off-label with some success to treat a number of dermatologic diseases, including several inflammatory skin conditions. Etanercept and infliximab might perhaps prove efficacious for inflammatory skin conditions as well. Finally, it is possible that drugs targeting TNF-alpha may have yet-unrecognized serious side effects. Because TNF-alpha seems to be a central cytokine in UVR-induced apoptosis, the chronic use of TNF-alpha-altering drugs might increase the risk for skin cancers. Tumor necrosis factor-alpha also plays some role in cutaneous wound healing; the effect these drugs might have on this process is also unknown at this time. Certainly, much is already [table: see text] known about TNF-alpha and how it plays many central roles. This understanding has allowed the development of

useful new drugs for intractable disease. As the understanding of TNF-alpha and other cytokine biology increases, so will the number of potential therapeutic agents.

Publication Types:

- Review
- Review, Academic

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1: Drugs 2000 Apr;59(4):745-51

Role of tumour necrosis factor-alpha in the progression of heart failure: therapeutic implications.

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The experimental and clinical evidence that demonstrates the effect of various cytokines, and in particular tumour necrosis factor (TNF)alpha, in patients with heart failure continues to accumulate. It is well established that increased levels of TNFalpha appear in the circulation of patients with heart failure and that the levels may have prognostic significance. Also, increased circulating TNFalpha levels may be responsible for the decreased expression of myocardial TNF receptors observed in failing myocardium. Along with these clinical data, it has been clearly demonstrated that increased levels of TNFalpha lead to cardiomyopathy and eventually death in experimental animals. Therefore, it is reasonable to assume that the increased levels of TNFalpha in patients with heart failure may be detrimental to cardiac function. The hypothesis that TNFalpha contributes to the pathogenesis of heart failure has recently been tested at the clinical level. The results of specific TNFalpha antagonism in patients with symptomatic heart failure demonstrate that anti-TNFalpha therapy is well tolerated and may be effective. This hypothesis is currently being tested in a large randomised, multicentre study that is expected to be complete within the next 2 years. Perhaps the most important aspect of the evolving research into the role of cytokines in heart failure is that the recognition of activation of inflammatory mediators provides new targets for therapeutic intervention.

Publication Types:

- Review
- Review, Tutorial

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

The role of TNF in cardiovascular disease.

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There is increasing evidence that cytokines in general and tumour necrosis factor (TNF) in particular play an important role in cardiovascular disease. This is not surprising since TNF modulates both cardiac contractility and peripheral resistance, the two most important haemodynamic determinants of cardiac function. Thus, increased levels of TNF or of its soluble receptors have been implicated in the pathophysiology of ischaemia-reperfusion injury, myocarditis, cardiac allograft and, more recently, also in the progression of congestive heart failure. In this later condition, TNF could be responsible for further ventricular remodelling; down-regulation of myocardial contractility; increased rate of apoptosis of the endothelial cell and of the myocytes, alteration of the expression and function of the enzymes regulating nitric oxide production and, of course, the induction of cachexia resulting in further peripheral muscle dysfunction. The hypothesis that TNF may be involved in the progression of CHF may be of clinical relevance as anti-TNF strategies are considered for therapeutical strategies. The purposes of this article are: (1) to define the physiological aspects of TNF; (2) to outline the specific function of TNF within the heart; (3) to consider the role of TNF in CHF; and (4) to speculate on possible anti-TNF treatment.1999 Academic Press@p$hr

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- Review
- Review, Tutorial

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Soluble tumor necrosis factor receptor abrogates myocardial inflammation but not hypertrophy in cytokine-induced cardiomyopathy.

Kubota T, Bounoutas GS, Miyagishima M, Kadokami T, Sanders VJ, Bruton C, Robbins PD, McTiernan CF, Feldman AM.

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BACKGROUND: Transgenic mice with cardiac-specific overexpression of tumor necrosis factor (TNF)-alpha develop dilated cardiomyopathy. The present study was designed to evaluate therapeutic effects of adenovirus-mediated neutralization of TNF-alpha on this model. METHODS AND RESULTS: An adenovirus encoding the 55-kDa TNF receptor-IgG fusion protein (AdTNFRI) was injected intravenously into 6-week-old transgenic mice, which resulted in high levels of TNFRI in both plasma and myocardium. AdTNFRI did not reverse cardiomegaly but abrogated myocardial inflammation. Furthermore, AdTNFRI blocked the myocardial expression of intercellular adhesion molecule-1 and downstream cytokines, including interleukin-1beta and monocyte chemotactic protein-1. Downregulation of alpha-myosin heavy chain was restored by the treatment, whereas upregulation of beta-myosin heavy chain was not reversed. In contrast, the downregulation of sarcoplasmic reticulum Ca(2+)-ATPase and phospholamban was normalized by AdTNFRI. Echocardiographic measurements showed that left ventricular end-systolic diameter was significantly larger in transgenic mice than in control mice, and this increase was reversed by the AdTNFRI treatment. However, left ventricular wall thickening was not reversed. CONCLUSIONS: These results suggest that anti-TNF therapy may hold promise in the treatment of end-stage heart failure.

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